DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

DEC 13 2004

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Re: Docket No. 1999P-1231/CP1

Dear Dr. Barbehenn, Mr. Sasich, Dr. Wolfe, and Ms. Pearson:

This letter responds to your citizen petition dated May 4, 1999, filed on behalf of Public Citizen's Health Research Group and the National Women's Health Network. You request that the Food and Drug Administration (FDA) require a patient medication guide (PMG) and revise the physician prescribing information (professional package insert) for tamoxifen (Nolvadex). Tamoxifen citrate tablets are approved currently for use in four indications: (1) treatment of advanced breast cancer, (2) adjuvant treatment of early breast cancer in women who have had surgery with or without radiation, (3) reduction in the risk of invasive breast cancer in women with ductal carcinoma in situ (DCIS)[1] following breast surgery and radiation, and (4) reduction in the incidence of breast cancer in women at high risk. Specifically, you request that FDA:

- Create two separate PMGs for tamoxifen based on two indications — treatment of advanced breast cancer and reduction in the incidence of breast cancer in women at high risk — and make other changes to the patient labeling, and

- Separate these two indications into distinct sections of the professional package insert (PI) for tamoxifen and make other changes to the PI.

[1] DCIS is non-invasive breast cancer treated with surgery or with surgery and radiation therapy. Tamoxifen is used to reduce the risk of the future development of invasive breast cancer after a diagnosis of DCIS in women treated with surgery and radiation therapy. Therefore, throughout this response, a distinction is made between women with breast cancer (i.e., invasive breast cancer that may be localized or advanced) and women with DCIS.

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FDA has considered information submitted in your petition and addresses your requests in this response. For the reasons explained below, your petition is granted in part and denied in part.

I. PATIENT MEDICATION GUIDE

You request that FDA require a PMG for tamoxifen. On October 29, 1998, FDA approved the use of tamoxifen to reduce the incidence of breast cancer in women at high risk for breast cancer. The final rule on medication guides for prescription drug products became effective on June 1, 1999 (21 CFR Part 208). Although the rule on PMGs was not in effect when tamoxifen was approved for any of its indications, patient labeling was created following the proposed rule's requirements for PMGs. This patient labeling (the patient package insert) was prepared to provide information in lay language to patients.

Section 208.1 of FDA's regulations (21 CFR 208.1) sets forth the requirements for patient labeling for human prescription drug products when FDA determines the drug product poses a "serious and significant public health concern requiring distribution of FDA-approved patient information." Section 208.1(c) provides that if any one of three circumstances exist, a PMG will be required:

(1) The drug product is one for which patient labeling could help prevent serious adverse effects.
(2) The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or continue to use, the product.
(3) The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

Because all three circumstances exist in the case of tamoxifen, FDA has determined that your request to substitute a PMG for tamoxifen for the current patient package insert is reasonable and appropriate. In fact, a PMG for tamoxifen was approved on June 10, 2003. Your specific requests regarding the content of this PMG are discussed below.

A. Separate Two Indications Into Two Separate PMGs

You request that FDA create two separate PMGs for two indications of tamoxifen: treatment of advanced breast cancer and reduction in the incidence of breast cancer in women at high risk. You state that having two PMGs would prevent the confusion that you believe occurs because readers find it difficult to discern what information is relevant to their particular indication.

The option of having two separate patient package inserts was considered at the time of approval of the risk reduction indication, but was rejected because of the choices patients have in filling

their tamoxifen prescription. A prescription for tamoxifen may be filled at any pharmacy, including mail-order prescription services. Physicians are not required to list the indication for which a product is being prescribed. If two separate PMGs were created, the choice of PMG would require that the pharmacist discuss the indication with the patient and select the appropriate medication guide for distribution. The use of mail-order prescription services would preclude any such discussion. Requiring pharmacists to select between two PMGs for the same product would impose an excessive and unrealistic burden on pharmacists and could lead to the distribution of the inappropriate PMG. For this reason, the Agency added specific statements to the PMG to emphasize the distinction between women with breast cancer and women at high risk for breast cancer and to clarify the intended audience for this document. The PMG includes the following statements:

- The subtitle of the approved PMG states "Written for women who use NOLVADEX to lower their high chance of getting breast cancer or who have ductal carcinoma in situ (DCIS)."

- The first sentence of the PMG states "This Medication Guide discusses only the use of NOLVADEX to lower the chance of getting breast cancer in high-risk women and in women treated for DCIS."

- A subsequent paragraph explains that women with breast cancer have different decisions to make about NOLVADEX and refers them to their doctor for further discussion.

- A sentence in a later section of the PMG reads "This guide does **not** discuss the special benefits and decisions for people who already have breast cancer."

- Under the heading **Why do women and men use NOLVADEX?**, the PMG again specifically lists the indications this document addresses.

The PMG therefore contains five separate references that describe its applicability only to women at high risk for breast cancer and women with DCIS. The PMG presents information for high-risk women in an easily discernable format.

While the risks associated with tamoxifen use are similar for all women, the anticipated benefit from use by a patient with breast cancer is greater. The first full paragraph of the PMG reflects this difference and states: "People taking NOLVADEX **to treat** breast cancer have different benefits and different decisions to make than high-risk women or women with DCIS taking NOLVADEX to reduce the chance of getting breast cancer. If you already have breast cancer, talk with your doctor about how the benefits of treating breast cancer with NOLVADEX compare to the risks that are described in this document." In addition, this decision reflects the fact that treatment for women with early or advanced breast cancer is complex and often involves more than one treatment or treatment modality — a discussion that is beyond the scope of a

PMG.

The Agency has considered your request for two separate PMGs and has determined not to separate the two indications for tamoxifen you requested be separated, the treatment of advanced breast cancer and reduction in the incidence of breast cancer in women at high risk, into two separate PMGs for the reasons stated above. Therefore, your request for two separate PMGs is denied.

B. For Each Indication, Clear Risk/Benefit Information Is Needed

You request that clear risk/benefit information be provided for each indication. The PMG clearly states that it is written for women at high risk for breast cancer and women with DCIS, not for women with breast cancer. The scope of the PMG is therefore confined to reducing the risk of invasive breast cancer and does not address benefit information for women who have already been diagnosed with this disease. In addition, the PMG states "Your doctor has a special computer program or hand-held calculator to tell if you are in the high-risk group." This statement conveys the need to formally calculate risk level and that only women at high risk should consider using Nolvadex.

Subsequent sections of the PMG discuss risk/benefit information for women at high risk for invasive cancer.

- The section **What is the most important information I should know about using NOLVADEX to reduce the chance of getting breast cancer?** states in bold type: **Because high-risk women don't have cancer yet, it is important to think carefully about whether the possible benefit of NOLVADEX in lowering the chance of getting breast cancer is greater than its possible risks**.

- Under the heading **What are the benefits of NOLVADEX to lower the chance of getting breast cancer in high-risk women and in women treated for DCIS?**, efficacy results from the randomized placebo-controlled studies submitted to FDA in support of the reduction in breast cancer in high-risk women and in women with DCIS are presented as both absolute and relative risk reductions.

- The section **What are the risks of NOLVADEX?** describes the serious side effects of Nolvadex.

- The limitations of our knowledge of the effects of Nolvadex are described in the section **What don't we know about taking NOLVADEX to reduce the chance of getting breast cancer?**

- Additional adverse events associated with Nolvadex are described in the section **What are the possible side effects of NOLVADEX?** This section provides more detail about the risk of side effects of tamoxifen, including the risk of blood clots, stroke, cataracts, and changes in the lining of the uterus. This section discusses early warning signs and when to contact a physician. For example, the labeling states: **Call your doctor right away if you have any signs of side effects listed below.**

The current PMG clearly presents the risk/benefit information a woman at high risk of breast cancer or with DCIS needs to consider. Therefore, your request is granted in part and denied in part.

C. Add a Clear Statement as to What Tamoxifen Does and Does Not Do

You ask that FDA add a clear statement as to what tamoxifen does and does not do.

The current PMG contains clear statements about what tamoxifen does do in three sections. Under the heading **What is the most important information I should know about using NOLVADEX to reduce the chance of getting breast cancer?**, the PMG states, "In the breast, NOLVADEX can block estrogen's effects. Because it does this, NOLVADEX may block the growth of breast cancers that need estrogen to grow (cancers that are estrogen- or progesterone-receptor positive.) NOLVADEX can lower the chance of getting breast cancer in women with a higher than normal chance of getting breast cancer in the next five years (high-risk women) and women with DCIS." The section **Why do women and men use NOLVADEX?** lists the uses of NOLVADEX and states, "NOLVADEX may keep the cancer from spreading to other parts of the body. It may also reduce the woman's chance of getting a new breast cancer."

The current PMG contains clear statements about what tamoxifen does not do in two different sections. Under the heading **What are the benefits of NOLVADEX to lower the chance of getting breast cancer in high-risk women and in women treated for DCIS?**, the PMG states "These studies do not mean that taking NOLVADEX will lower your personal chance of getting breast cancer. We do not know what the benefits will be for any one woman who takes NOLVADEX to reduce her chance of getting breast cancer." The section **What don't we know about taking NOLVADEX to reduce the chance of getting breast cancer?** includes the following statements:

We don't know:

- if NOLVADEX lowers the chance of getting breast cancer in women who have abnormal breast cancer genes (BRCA1 and BRCA2)
- if taking NOLVADEX for 5 years reduces the number of breast cancers a woman will get in her lifetime or if it only delays some breast cancers
- if NOLVADEX helps a woman live longer

- the effects of taking NOLVADEX with hormone replacement therapy (HRT), birth control pills, or androgens (male hormones)
- the benefits of taking NOLVADEX if you are less than 35 years old

Studies are being done to learn more about the long-term benefits and risks of using NOLVADEX to reduce the chance of getting breast cancer.

The Agency believes these statements clearly explain what tamoxifen does and does not do. Therefore, your request is granted.

D. Revise the Description of the Royal Marsden Study (RMS) for Reduction in the Incidence of Breast Cancer for Women at High Risk

You request that FDA revise the description of the RMS in the PMG for reduction of incidence in breast cancer. The Agency notes that there is no description of the RMS in the PMG, therefore your question becomes whether to include a description of the RMS in the PMG. You state that the RMS, although different in some respects from the P-1 trial that was the basis for approval of tamoxifen, had the power to detect a tamoxifen "preventive" effect, had one existed.

The RMS was begun in 1986 as a feasibility study of whether larger scale trials could be mounted. The trial was subsequently extended to a pilot trial to accrue additional participants to further assess the safety of tamoxifen. A total of 2,471 women were entered between 1986 and 1996.

FDA considered the study design and published findings and determined that several factors may have contributed to the results of the study, including the following:

- Only about 20 percent of the women in the study were likely to have mutations in breast cancer genes BRCA-1 or BRCA-2. The assumptions regarding risk and number of events used to calculate sample size were incorrect, resulting in a study that was underpowered to detect a difference.

- Many women were young at the time of study entry (66 percent younger than age 50), so a difference may not have appeared because it may not be detected until most of these women are age 60 or older.

- Younger women are more likely to have estrogen receptor negative tumors, whose development is unaffected by tamoxifen treatment.

- The use of hormone replacement therapy in this trial was a confounding factor.

- It appears that the RMS did not take probable annual noncompliance rates into account when powering the study.

Adding a description of the RMS is beyond the scope of the PMG and would mislead consumers. The current PI provides health care providers (and consumers if they choose to read the PI) with the results of these trials and a brief, but clear, explanation of why the Agency believes the results of the RMS study were different from the P-1 trial. It would be appropriate for women to raise any questions about these studies with their physician for a better understanding of the study results. The Agency does not agree with your statement that the RMS had the power to detect a tamoxifen preventative effect and denies your request to include a description of that study in the PMG.

E. Remove Repetitive Information

You request that FDA remove repetitive information from the PMG, stating that repetition creates confusion and makes it difficult for the reader to discern what is really important. Your petition does not provide specific examples of repetitive information. The Agency's review of the PMG found that only information on risk is presented in several different sections. It is appropriate, given the importance of this information, to re-state the risks of tamoxifen therapy in all relevant sections of the PMG. Therefore, the Agency has no plans to delete this information. Your request to remove repetitive information from the PMG is denied.

F. Add Information From Other Tamoxifen Studies

You request that the Agency add information about possible adverse events not monitored in the P-1 trial, including ocular toxicity and uterine pathology, and you provide six references to support your statement. You state that in the P-1 trial, baseline endometrial sampling was optional for 11,000 out of the approximately 13,000 women enrolled and eye exams were not required. You therefore conclude that FDA does not have reliable incidence data from this study on those adverse effects.

The P-1 trial enrolled the largest group of women studied in a prospective, randomized, double-blind, placebo-controlled trial of tamoxifen and provides the best documentation of tamoxifen-related side effects. All women were required to have baseline and follow-up gynecologic examinations with work-up of any reported abnormality. Women were asked at baseline and each follow-up visit about visual changes and ophthalmologic events. The P-1 trial also included a substudy that evaluated whether routine endometrial sampling increased cancer detection rates or provided other benefits. This study showed that routine sampling increased the number of invasive procedures without increasing the diagnostic rate of uterine cancer or other clinically significant abnormalities. An ophthalmologic substudy performed in NSABP B-14 did not detect any eye findings relevant to the use of Nolvadex other than cataracts. Information on cataract

formation and surgery was collected and analyzed in P-1. The PMG includes the "adverse reactions reasonably likely to be caused by the drug product that are serious or occur frequently," consistent with the requirements for a medication guide (21 CFR 208.20 (b)(7)(I)). The references you provide describe eye and endometrial findings in small studies or case series that have not been substantiated in larger controlled trials.

FDA has reviewed the section of the PMG under the heading **What are the possible side effects of NOLVADEX?** and has determined that all eye and endometrial adverse events that are appropriate are currently listed. Therefore, your request is denied.

G. Add Exclusion Criteria That Were Used in the P-1 Trial

You request that FDA include exclusion criteria that were used in the P-1 trial and are not in the current labeling, including the following:

- Life expectancy less than 10 years
- Prior or suspected breast cancer of any type: invasive; ductal carcinoma *in situ* (DCIS) or lobular carcinoma *in situ* (LCIS) treated with mastectomy, radiation, or systemic adjuvant therapy
- Prior malignancy less than 10 years ago, except carcinoma *in situ* (CIS) of the cervix or basal/squamous cell carcinoma of the skin
- Existing nonmalignant disease which precludes use of tamoxifen
- Performance status that restricts normal therapy
- Estrogen or progesterone replacement therapy, oral contraceptives, androgens (unless stopped 3 months before taking tamoxifen)
- Prior use of tamoxifen
- Prior history of macular degeneration
- Concurrent use of chemotherapy
- Refusal to undergo endometrial sampling or unsuccessful sampling (if the woman has an intact uterus)

Most of the criteria you list were written to exclude women with other medical illnesses or who use other medications that could affect the detection of subsequent breast cancer or could result in an inaccurate assessment of tamoxifen-related toxicities, and do not affect the conclusions of the study. Such criteria include life expectancy less than 10 years, prior or suspected breast cancer of any kind, prior malignancy within 10 years, and prior use of tamoxifen or concurrent use of chemotherapy. Because the purpose of clinical trials is to obtain clear, unconfounded information on whether a drug is safe and effective in treating a particular disease or condition, clinical trials are conducted under very precise and controlled conditions. Not all of these conditions are necessarily applicable to the administration of an approved drug product in general medical use.

While women with a prior history of macular degeneration were excluded from the trial, an ocular substudy from the NSBP B-14 and data collected during the P-1 trial did not demonstrate an increased incidence of macular degeneration with tamoxifen use. For this reason, macular degeneration is not considered a contraindication to tamoxifen therapy. Women with this condition are not excluded from the ongoing Study of Tamoxifen and Raloxifene (STAR) trial.

Women who refused endometrial sampling were also excluded from the trial. In the P-1 trial, endometrial sampling did not increase the ability to detect endometrial cancer. Endometrial sampling is not recommended for women on tamoxifen therapy. This issue was discussed at the Oncology Drug Advisory Committee meeting in September of 1998; nine members of the committee voted not to include endometrial sampling in future studies, and two abstained from voting. Endometrial sampling is not required in the STAR study.

The criterion "existing nonmalignant disease which precludes the use of tamoxifen" is addressed by the exclusions listed under the heading **Who should not take NOLVADEX?**

Your request to note the exclusion "estrogen or progesterone replacement therapy, oral contraceptives, androgens (unless stopped 3 months before taking tamoxifen)" is addressed in the Medication Guide under the heading **What don't we know about taking NOLVADEX to reduce the chance of getting breast cancer?** with the statement "We don't know the effects of taking NOLVADEX with hormone replacement therapy (HRT), birth control pills, or androgens (male hormones)." Additional warnings to avoid the use of oral contraceptives are included under the heading **What should I avoid while taking NOLVADEX?**

Your request to note the exclusion "performance status that restricts normal activity for a significant portion of the day" is addressed in the section **Who should not take NOLVADEX?** with the statement "Do not take NOLVADEX to lower your chance of getting breast cancer if: Your ability to move around is limited for most of your waking hours."

Adequate information about appropriate exclusion criteria are present in the PMG. Therefore, your request to add additional information is denied.

H. Add a Clear Statement as to Who Should and Should Not Take Tamoxifen

You request that FDA add a clear statement as to who should and should not take tamoxifen. Under the heading **Who should not take NOLVADEX?**, the current PMG lists a series of statements about who should not take tamoxifen. These statements include:

Do not take NOLVADEX for any reason if you

- **Are pregnant or plan to become pregnant while taking NOLVADEX or during the 2 months after you stop taking NOLVADEX. NOLVADEX may harm your unborn baby.** It takes about 2 months to clear NOLVADEX from your body. To be sure you are not pregnant, you can start taking NOLVADEX while you are having your menstrual period. Or, you can take a pregnancy test to be sure you are not pregnant before you begin.
- **Are breast feeding.** We do not know if NOLVADEX can pass through your milk and harm your baby.
- **Have had an allergic reaction to NOLVADEX or tamoxifen** (the other name for NOLVADEX), or to any of its inactive ingredients.

If you get pregnant while taking NOLVADEX, stop taking it right away and contact your doctor. NOLVADEX may harm your unborn baby.

Do not take NOLVADEX to lower your chance of getting breast cancer if:

- You ever had a blood clot that needed medical treatment.
- You are taking medicines to thin your blood, like warfarin, (also called Coumadin®).
- Your ability to move around is limited for most of your waking hours.
- You are at risk for blood clots. Your doctor can tell you if you are at high risk for blood clots.
- You do not have a higher than normal chance of getting breast cancer. Your doctor can tell you if you are a high-risk woman.

In addition, there are a series of statements that inform women that tamoxifen has not been tested in women under age 35 or in women with BRCA 1 or 2 mutations.

The Agency has reviewed the PMG in response to your request and has determined that the current labeling appropriately addresses who should and should not take tamoxifen. Therefore, your request is denied.

I. Emphasize the Increased Incidence of Serious Adverse Effects in Women Over 50

You request that FDA modify the PMG to emphasize the increased incidence of serious adverse effects in women over age 50. FDA's review of the primary data for the P-1 trial indicated that the relative risk of developing a serious adverse event was similar between women over 50 and women under 50. However, the absolute risk was greater in women over 50. The number of events compared with the number of study participants was small, precluding meaningful statistical subset analysis. It is important to emphasize in the PMG and in the physician labeling that all women, not only women over 50, are at risk for serious adverse effects. Therefore, your request is denied.

J. Add a Contraindication for Nursing Mothers

You request that FDA add a contraindication for nursing mothers. Under the heading **Who should not take NOLVADEX?**, the current PMG states in a separate bulleted listing "Do not take NOLVADEX for any reason if you are breast feeding." This is a clear statement that women who are nursing an infant with their own breast milk should not take tamoxifen. Therefore, your request is granted.

K. Add a Clarification of the Limitations of the Gail Model

You request that FDA add a clarification of the limitations of the model used to predict breast cancer risk (the Gail model).

The Gail model is a computer model developed to predict breast cancer risk and is the only model that accounts for the interaction of different risk factors. It is the best validated model, both in previous small studies and in the P-1 trial itself. The Gail model is addressed in the PMG under the heading **Why should I read this Medication Guide?** In their original paper (*JNCI* 81:1879-86, 1989), Gail and colleagues noted that identification of other breast cancer risk factors could contribute to a better model. Based on subsequent identification of atypical hyperplasia as a risk factor, Gail introduced an adjustment for this factor. Gail also noted that the model is applicable to women with a normal breast exam and mammogram who return for regular follow-up. The model overestimates risk in younger women (age less than 64) who have sporadic follow-up. The model may overestimate risk in women with extensive family histories of breast cancer (Vogel et al., *Oncology* 10:1451-58, 1996). The PMG emphasizes the need for regular examinations and mammograms and specifically states that the effect of Nolvadex in women with BRCA1/2 mutations is unknown.

FDA has reviewed your request and has decided to emphasize that the reduction of incidence indication is intended for women at high risk. Therefore, FDA added to the title of the PMG the phrase "Written for women who use NOLVADEX to lower their high chance of getting breast cancer or who have ductal carcinoma in situ (DCIS)" to make it clear that the reduction of incidence indication is for women at high risk. FDA also added information to convey that a health care professional using a Gail Model Risk Assessment Tool (described in lay language) can calculate whether a woman is at high risk. This will introduce the concept of risk/benefit analysis early on in the PMG and facilitate discussion between a woman and her doctor about her risk as calculated using the Gail model. The Agency believes that further discussion regarding the limitations of the Gail Model is beyond the scope of the PMG and should be the subject of discussion between a woman and her doctor. Therefore, your request is granted in part and denied in part.

II. PROFESSIONAL PACKAGE INSERT

You request that FDA revise the PI, which you refer to as the *physician label.* Your specific requests for revisions to the PI are discussed below.

A. Separate Two Indications Into Clearly Distinct Sections of the Labeling

You request that FDA separate two of tamoxifen's indications, treatment of breast cancer and reduction of incidence of breast cancer, into clearly distinct sections of the PI. In September 1998, the **Clinical Studies** section of the PI was reorganized as follows:

- Metastatic breast cancer
  - — Premenopausal women
  - — Male breast cancer

- Adjuvant breast cancer
  - — Node positive
  - — Node negative
  - — Duration of therapy
  - — Contralateral breast cancer

- Reduction in breast cancer incidence in women at high risk

In December 1999, the indication for reduction in the risk of invasive breast cancer in women with DCIS was added to the PI before the reduction in breast cancer incidence indication. This order was followed within each of the sections of the labeling required in 21 CFR 201.56(d) and as described in 21 CFR 201.57, including **Clinical Pharmacology** and **Indications and Usage.** You suggest that these headings should be listed twice, once for breast cancer and once for

reduction in the incidence of breast cancer for women at high risk. We believe it would be confusing and repetitious to list these headings twice in the labeling. Therefore, your request is denied.

B. Add Clear Risk/Benefit Information for Each Indication

You request that FDA add clear risk/benefit information for each indication. FDA has reviewed the risk/benefit information in the labeling and believes that this information is presented clearly in tables provided in the **Clinical Pharmacology** section. For example, Table 3: Major Outcomes of the NSABP P-1 Trial summarizes the major outcomes of the P-1 trial and presents data on relative risk between Nolvadex and placebo. The table presents risk outcomes according to individual risk factors and overall level of risk. Table 4 provides information about tumor characteristics and stage of diagnosis for women who developed breast cancer. Table 1 summarizes the major outcomes of the NSABP B-24 trial (placebo-controlled study of Nolvadex in women with DCIS treated with lumpectomy and radiotherapy). The rates and relative risks of invasive breast cancers and other important efficacy and safety endpoints are presented. Because the Agency believes clear risk and benefit information is presented in the PI, your request is denied.

C. Include the Complete Reference Along With Each Study Cited

You request that FDA include the complete reference along with each study cited, not just the name of the senior author or name of the trial, so that a reader can retrieve the source document. Complete references, other than those dealing with safe drug handling, generally are not included in the labeling of drug products. Therefore, your request is denied.

D. Include Data to Support Claims

You request that FDA include data to support claims. In particular, you mention that no data are presented to support the statement that the Nolvadex Adjuvant Trial Organization (NATO) study demonstrated improved disease-free survival and that no data are provided to support the statement that Nolvadex is effective for the male breast cancer indication.

Under the heading **Clinical Studies - Adjuvant Breast Cancer**, the labeling includes a detailed description of survival and proportional reductions in mortality taken from the overview analysis. The overview provides the best estimates of these figures. FDA does not agree that adding data from the NATO study and the other studies mentioned in this section will provide additional useful information to the practitioner.

Male breast cancer is a rare event with few published trials. In the **Clinical Pharmacology** section of the labeling, which discusses clinical studies on metastatic breast cancer, the response

rate for 132 patients is discussed. A current reference search identified small retrospective trials or case reports/series on male breast cancer. Some of these articles reported response rates, and some did not. No information about time to progression (TTP) or other traditional endpoints was available. The **Adverse Reactions** section of the labeling refers to reports from the literature and case reports that suggest that the safety profile of Nolvadex in males is similar to that seen in women. This section also includes the statements "Loss of libido and impotence have resulted in discontinuation of tamoxifen therapy in male patients. Also, in oligospermic males treated with tamoxifen, LH, FSH, testosterone and estrogen levels were elevated. No significant clinical changes were reported."

FDA has reviewed your request and has determined that additional data to support these two claims will not improve on information already included in the PI. Therefore, your request is denied. Should new research on male breast cancer emerge, FDA will review whether any such data warrant being added to the labeling.

E. Revise the Description of the Royal Marsden Study (RMS)

You request that FDA revise the description of the RMS for reduction of incidence in breast cancer in the PI. This request is similar to your request for revisions to the patient package insert/PMG addressed in section I.D of this response. The RMS is discussed in the **Clinical Pharmacology** section of the PI. This section explains that the statistical power of the study was reduced because few breast cancer events occurred during the study. The section also provides possible reasons why the RMS may not have provided an adequate assessment of the effectiveness of tamoxifen in reducing the incidence of breast cancer. FDA considers the description of the study to be accurate and adequate. For the reasons explained above, your request that FDA revise the description of the RMS is denied.

F. Remove Repetitive Information

You request that FDA remove repetitive information from the PI. In September of 1998, FDA reviewers eliminated outdated information, removed adverse events not related to tamoxifen administration, and reorganized the labeling by indication. You do not give specific examples of information you consider repetitive in the PI. FDA does not agree that the labeling currently consists of repetitive information that makes the labeling confusing or difficult to understand. Therefore, your request is denied.

G. Add Information From Other Tamoxifen Studies Including Possible Adverse Events Not Monitored in the P-1 Trial

You request that FDA add information from other tamoxifen studies, including possible adverse events not monitored in the P-1 trial, such as ocular toxicity and uterine pathology. You note that in the P-1 trial, eye exams were not required of the approximately 13,000 women enrolled in the

trial, and baseline endometrial sampling was optional for 11,000 out of the 13,000 women enrolled in the trial.

The **Warnings** section of the PI contains a comprehensive listing of adverse events. This list includes events specific to metastatic breast cancer patients, malignant and nonmalignant effects on the uterus, thromboembolic events, malignant and nonmalignant effects on the liver, other cancers, effects on the eye, and pregnancy warnings. The **Adverse Reactions** section of the labeling contains information about adverse events organized by stage of disease.

FDA has reviewed the labeling and concludes that the warnings, precautions, and adverse reactions listed are comprehensive based on the best scientific data currently available. Therefore, your request to add information from other tamoxifen studies to the PI is denied.

H. Add Exclusion Criteria That Were Used in the P-1 trial and That Are Not in the Current Labeling

You request that FDA add to the PI exclusion criteria that were used in the P-1 trial and are not in the current labeling. This request is the same as your request that FDA take this action in the patient package insert or PMG. FDA's response to your request is discussed in section I.G. Furthermore, the PI contains information and warnings about which patients are appropriate for Nolvadex use. The PI states that nonhormonal contraception must be used in the **Pregnancy Category D** and **Information for Patients** sections. The PI contains multiple warnings about the risk of thromboembolic disease in women who take Nolvadex. These warnings provide sufficient information to health care providers about the potential risk in patients with decreased performance status. The PI also describes other risks of Nolvadex and informs patients and health care providers that a woman's personal health history is important in determining whether the risks of Nolvadex outweigh its benefits for an individual. Therefore, your request is denied.

I. Add a Clear Statement as to Who Should and Should Not Take Tamoxifen

You request that FDA add to the PI a clear statement as to who should and should not take tamoxifen. Information on who should and should not take tamoxifen is found in six sections of the current PI: the **Clinical Studies** section, the **Indications and Usage** section, the **Contraindications** section, the **Warnings** section (including Pregnancy Category D warnings), the **Information for Patients** section, and the **Drug Interactions** section. The current labeling contains clear statements about who should and should not take tamoxifen and thus further information is not required. Therefore, your request is denied.

J. Express Drug Levels in Animal Studies as Multiples of the Human Exposure Based on Surface Area

You request that FDA express drug levels in animal studies as multiples of the human exposure based on surface area (not milligrams/kilogram). FDA agrees with your request. This information in the labeling has been updated. Therefore, your request is granted.

K. Emphasize the Increased Incidence of Serious Adverse Effects in Women Over 50

You request that FDA emphasize the increased incidence of serious adverse effects in women over 50. You also request that FDA make this same change to the PMG. As discussed previously in section I.I of this response, FDA believes it is important to emphasize in both the PMG and in the PI that all women are at risk for serious adverse effects, not only women over 50. Therefore, your request is denied.

L. Add a Contraindication for Nursing Mothers

You request that FDA add a contraindication for nursing mothers to the PI. In the **Precautions** section of the PI, there is a paragraph labeled **Nursing Mothers**. This paragraph states "It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from NOLVADEX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother." However, FDA is pursuing changes to the **Contraindications** section of the PI with the manufacturer of Nolvadex in order to make the labeling consistent.

M. Add a Clarification of the Limitations of the Gail Model

You request that FDA add a clarification of the limitations of the Gail model to the PI. You state that research using a very large database has found that the Gail model overpredicts the risk of breast cancer. You state that the Gail model omits any discussion of factors that may decrease risk and that may be equally important in a woman's decision to use or not use tamoxifen. This request is similar to your request that this clarification be made in the patient package insert/PMG, as discussed in section I.K of this response.

As previously discussed, the Gail model is the best validated model to predict breast cancer and is the only model that accounts for the interaction of different risk factors for breast cancer. Gail and colleagues noted in their original paper that identification of other breast cancer risk factors could contribute to a better model (*JNCI* 81:1879-86, 1989). Based on subsequent identification of atypical hyperplasia as a risk factor, Gail introduced an adjustment for this factor. Gail also

noted that the model is applicable to women with a normal breast exam and mammogram who return for regular follow-up. The model may overestimate the risk in women with extensive family histories of breast cancer (Vogel et al., *Oncology* 10:1451-58, 1996).

Based on results of the NSABP P-1 study, the Gail model (part of the Nolvadex label) was updated to correct the overestimation of risk in Hispanic women.

The Gail model is discussed in the **Indications and Usage** section of the PI. The **Indications and Usage** section, under the heading **Reduction in Breast Cancer Incidence in High Risk Women**, includes a thorough discussion stating that Nolvadex is indicated only for women at high risk. Women at high risk are defined as women at least 35 years of age with a 5-year predicted risk of breast cancer greater than or equal to 1.67 percent, as calculated by the Gail model. Examples of combinations of risk factors at specific ages predicting a 5-year risk at 1.67 percent are provided. Following this comprehensive list, the labeling states that for women whose risk factors are not described in the examples provided, the Gail model is necessary to estimate absolute breast cancer risk, and a toll-free number is provided for health care professionals to obtain a Gail Model Risk Assessment Tool. Following a statement that no data are available regarding the effect of Nolvadex on breast cancer incidence in women with inherited mutations, the PI states:

> After an assessment of the risk of developing breast cancer, the decision regarding therapy with NOLVADEX for the reduction in breast cancer incidence should be based upon an individual assessment of the benefits and risks of NOLVADEX therapy. In the NSABP P-1 trial, NOLVADEX treatment lowered the risk of developing breast cancer during the follow-up period of the trial, but did not eliminate breast cancer risk . . . .

While methods to decrease the risk of breast cancer, including following a low-fat diet, minimizing alcohol consumption, or prophylactic mastectomy, have been discussed in the literature, with the exception of prophylactic mastectomy, none of these strategies has been scientifically shown to be effective. Any discussion of the risks and benefits of alternative therapeutic choices versus the risks and benefits of taking tamoxifen should occur between a woman and her health care provider in the context of her treatment decisionmaking process.

The current PI adequately addresses the Gail model. The **Indications and Usage** section of the labeling clearly states that Nolvadex is indicated for use in women at high risk. This section also states that the decision regarding therapy for the reduction in incidence of breast cancer for women at high risk should be made based on an individual assessment of the benefits and risks of therapy. For the reasons discussed above and in section I.K of this response, your request to add a clarification of the limitations of the Gail model to the PI is denied.

N. Address Problems With Emphasizing Absolute Number to Determine Whether to Start Tamoxifen

You state that the emphasis on an absolute number (1.7 percent over 5 years) to determine whether to start tamoxifen is misleading since the National Cancer Institute (NCI) admits that "other risk factors for breast cancer have been identified or proposed . . .", although NCI has not been able to incorporate those factors into their calculations. You state that in the P-1 trial, women with a 5-year predicted risk of breast cancer of 2.0 to 5.0 percent taking tamoxifen were not statistically better off after treatment than women with a similar 5-year risk receiving placebo, indicating a weak predictive relationship.

The Gail model does not include all known risk factors, but it is one of only a few models that account for the interaction of different risk factors. It is also the best validated model, both in previous small studies and in the P-1 trial itself. At present, it is the best available breast cancer risk assessment tool.

The P-1 trial is the only randomized, prospective, double-blind, placebo-controlled study in high-risk women that has been completed and submitted to the Agency for review. Its entry criteria were based on the 1.7 percent incidence figure, and tamoxifen significantly decreased breast cancer incidence in all prospectively defined groups. The following results analyzed by risk level were obtained from the NSABP's publication with updated data (*JNCI* 90:1371-88, 1998).

Table 1. Average annual hazard rates for breast cancer by 5-year predicted risk

5-year predicted breast cancer risk (%)	Number of Events		Rate/1,000 Women		Risk ratio (rr)	95% CI
	Placebo	Tamoxifen	Placebo	Tamoxifen		
≤2.00	35	13	5.54	2.06	0.37	0.18-0.72
2.01-3.00	42	29	5.18	3.51	0.68	0.41-1.11
3.01-5.00	43	27	5.88	3.88	0.66	0.39-1.09
≥5.01	55	20	13.28	4.52	0.34	0.19-0.58

Although the confidence intervals overlap 1.00 for women with a 5-year risk of 2.01-5.00 percent, the upper bound is close to one. The study was prospectively stratified by relative risk but not by absolute risk, and was not powered for subset analysis. The results in these risk groups are consistent with the findings identified in lower and higher risk groups and with the results seen in the entire randomized trial. These data show consistent evidence of benefit in all groups. Therefore, your request is denied.

O. Revise Data Presentation

In the conclusions section of your petition, you raise an issue about the presentation of data in the tamoxifen labeling. You request that FDA convert the risks and benefits of tamoxifen therapy by calculating the "number needed to treat." The labeling presents the risks and benefits of tamoxifen therapy by number of cases per year per 1,000 women taking tamoxifen. We acknowledge that it is important, and sometimes difficult, to present data in terms easily understandable to the lay public. This task usually is accomplished by using percentages. However, because of the small number of events in a large trial population, this approach was not feasible for tamoxifen. We chose to use cases per 1,000, which is not substantially different from your suggested approach of cases per 100.

III. CONCLUSIONS

Your request to substitute a PMG for the current patient package insert for tamoxifen is granted; in fact, the PMG was approved on June 10, 2003. For the reasons explained above, your request for two separate PMGs is denied. Our responses to your specific requests regarding the content of the PMG and the PI are discussed above.

Therefore, for the reasons discussed above, your petition is granted in part and denied in part.

Sincerely,

Steven K. Galson, M.D., M.P.H.
Acting Director
Center for Drug Evaluation and Research